60. (new) The method of claim 59, wherein the blood sample is selected from the group consisting of whole blood, plasma, platelets, packed red blood cells, bone marrow, lymphocytes, and serum.

61. (new) The method of claim 59, wherein the nucleic acid probe is selected from the group consisting of: GCTGCTTCCTTCCGGACCTGAC (SEQ ID NO:2); GCTGCTTCCTTCCGGACCTGA (SEQ ID NO:3); GGCACACGCGTCATCTGC (SEQ ID NO:9); GCTGCTTCCTTC (SEQ ID NO:4); GCTGCTTCCTTCCGGACCTGAGTGAATACGTTCCCGGGCCT (SEQ ID NO:7); GCTGCTTCCTTCCGGACCTGACAAAAACGATAAACCAACCA (SEQ ID NO:8); GCTGCTTCCTTCCGGACCTGACCTGGTAAA (SEQ ID NO:11); GCTGCTTCCTTCCG (SEQ ID NO:5); GACCTGACCTGGTA (SEQ ID NO:6); GCTGCTTCCGTC (SEQ ID NO:21); CGGACCTGACCTG (SEQ ID NO:22); AGGACCUGACAUG (SEQ ID NO:23); CGGACCUGACCAG (SEQ ID NO:24); CGGACCUGACAAG (SEQ ID NO:25); and CGGAUCUGACACG (SEQ ID

62. (new) The method of claim 59, wherein the first nucleic acid probe is an adaptor probe comprising a subsequence that hybridizes under stringent conditions to the gel-immobilized probe.

63. (new) The method of claim 62, wherein the adaptor has a nucleotide sequence selected from the group consisting of: GCTGCTTCCTTCCGGACCTGAGTGAATACGTTCCCGGGCCT (SEQ ID NO:7); and GCTGCTTCCTTCCGGACCTGACAAAAACGATAAACCAACCA (SEQ ID NO:8).

REMARKS

With this amendment, claims 1-43 and 51-63 are pending in the present application and are currently under examination. Claims 1-43 were examined. Claims 1, 20-22,

24, 26-32, 41, and 42 were amended. New claims 51-63 were added. For convenience, the Examiner's rejections are addressed in the order in which they were presented in the May 8, 2000 Office Action.

Status of the claims

Claims 1, 20-22, 24, 26-32, 41, and 42 were amended to provide sufficient antecedent basis for certain claim terms. These amendment adds no new matter.

Claims 51 recites a nucleic acid probe that is perfectly complementary to the SRP RNA. This amendment adds no new matter. Support for this amendment can be found, e.g., in the specification on page 9, lines 11-14.

Claims 52 and 54 were added to recite a method of detecting a bacterium with a probe that is perfectly complementary to a bacterial SRP RNA, wherein the probe is 8-50 nucleotides in length. These claims add no new matter. Support for these claims can be found, e.g., in claims 6 and 17 as originally filed, and in the specification on page 9, lines 11-14.

Claims 53, 55, 58, and 61 were added to recite specific nucleic acid probes. These claims add no new matter. Support for these claims can be found, e.g., in claim 19 as originally filed.

Claim 56, 57, 59, and 60 were added to recite methods of detecting a bacterium in a human blood sample. These claims add no new matter. Support for these claims can be found, e.g., in the specification on page 16, lines 30-31.

Claims 62 and 63 were added to recite adaptor probes. These claims add no new matter. Support for these claims can be found, e.g., in claims 42 and 43 as originally filed.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 1-43 were rejected as allegedly indefinite. Applicants respectfully traverse. According to MPEP § 2173.02, whether or not a claim meets the threshold requirements of clarity and precision under § 112, second paragraph, is assessed in light of (A) the application specification, (B) the teachings of the prior art, and (C) the interpretation that

would be given by one of skill in the art at the time of invention. Applicants submit that in light of these factors the claimed invention meets the threshold requirements of clarity and precision under § 112, second paragraph.

"Final process step"

Claims 1-43 were rejected as allegedly indefinite for failing to recite a final process step which "agrees back with the preamble." As the Examiner helpfully suggested, Applicants have amended the claims to recite a final step "wherein hybridization of the probe is indicative of the presence of said non-viral organism." Applicants therefore respectfully request that the rejection be withdrawn.

"Substantially complementary"

Claims 1-43 were rejected as allegedly indefinite for reciting the term "substantially complementary." The rejection alleges that although the term is defined in the specification on page 9 and refers to nucleic acids that hybridize under "stringent conditions" to a target, the specification lacks a "clear definition." Applicants respectfully traverse.

In the context of the hybridization reactions of the invention, which use oligonucleotides as probes, one of skill in the art would understand the phrase "stringent hybridization conditions" as referring to standard conditions for such reactions. Oligonucleotides that hybridize under such conditions are considered to be substantially complementary to the target, as defined, e.g., in the specification on page 9, lines 6-10. The use of these phrases thereby meeting the threshold clarity and precision standards of the statute. MPEP § 2173.02. As described by the court in *In re Chilowsky*,

> It is well settled that the disclosure of an application embraces not only what is expressly set forth in words or drawings, but what would be understood by persons skilled in the art. . . . That which is common and well known is as if it were written out in the patent. *In re Chilowsky*, 108 USPQ 321, 324 (C.C.P.A. 1956).

The present application discloses to the use of oligonucleotide probes and adaptors to identify SRP nucleic acids. The present application further discloses prior art materials that teach standard conditions for reactions using such probes (*see, e.g.*, specification page 10, lines 2-4, referring, e.g., to Tijssen, *Techniques in Biochemistry and Molecular Biology--Hybridization with Nucleic Probes*, "Overview of principles of hybridization and the strategy of nucleic acid assays" (1993)). One of skill in the art would therefore clearly understand that phrases "substantially complementary," and "stringent conditions," as used in the context of hybridization reactions using oligonucleotide probes and adaptors, refer to standard stringent hybridization conditions known to those of skill in the art. Applicants therefore respectfully request that the rejection be withdrawn.

"The nucleic acid probe"

Claim 22 was rejected as allegedly indefinite for reciting "the nucleic acid probe," on the basis of insufficient antecedent basis. Applicants have amended the claims to provide sufficient antecedent basis. Applicants therefore respectfully request that the rejection be withdrawn.

"Step of contacting

Claims 24 and 25 were rejected as allegedly indefinite because the "step of contacting" has insufficient antecedent basis. To expedite prosecution, Applicants have amended the claims to provide sufficient antecedent basis. Applicants therefore respectfully request that the rejection be withdrawn.

"Duplex SRP RNA"

Claim 27 was rejected as allegedly indefinite because the term "duplex" nucleic acid conflicts with step (v) of the base claim. To expedite prosecution, Applicants have amended the claim to recite "a duplexed SRP RNA" instead of "the duplex SRP RNA." Applicants also point out that there is no conflict with step (v) of the base claim. When the immobilized probe

captures the duplexed SRP RNA, it displaces the first nucleic acid probe, thereby forming a duplexed SRP RNA Applicants therefore respectfully request that the rejection be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph: written description

Claims 14, 16, 18, 36, 38, and 40 were rejected as allegedly lacking written description. In the Office Action, the Examiner observed that the purpose of the written description requirement is to convey to one of skill in the art that the inventor was in possession of the invention as of the filing date. The rejection then stated that the practice of the invention requires knowledge of specific SRP RNA sequences that "would not have been known to one of ordinary skill in the art at the time the invention was made." Office Action, page 5, lines 6-7. Applicants respectfully traverse the rejection.

The claims fully comply with the requirements for written description of a chemical genus, e.g., a nucleic acid genus, as set forth in *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997). As described by the Federal Circuit in *Lilly*, "[a] description of a genus of cDNAs may be achieved by means of . . . a recitation of structural features common to the members of the genus . . . ." *Lilly*, 43 USPQ2d at 1406. Furthermore, the court in *Fiers v. Revel* stated that an adequate written description "requires a precise definition, such as by structure, formula, chemical name, or physical properties." *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). As the specification describes hybridization conditions, discloses methods of aligning SRP RNAS, and references 4.5S and 7S SRP sequences to which members of the claimed nucleic acid genus hybridize, the claimed sequences are thereby defined via shared physical and structural properties.

The present invention relates to methods of detecting SRP RNA, using oligonucleotide probes that are substantially complementary, i.e., hybridize under stringent conditions, to the target SRP RNA. The genus of SRP RNA probes is therefore described by reference to shared structural features, i.e., the ability to hybridize under stringent conditions to SRP nucleic acid sequences. The specification on page 14 discloses that sequences for SRP RNA can be obtained through publicly available databases, such as GenBank or a web site at

http://www.medkem.gu.se/dbs/SRPDB/. In addition, the specification references a journal article that provides an alignment of SRP RNAs (Larsen & Zweib, specification, page 14, lines 15-16), as well as providing sequence alignment algorithms. As described in the specification, the SRP RNAs are highly conserved. Therefore, if a specific SRP RNA is desired, it can be cloned and sequenced according to standard techniques known to those of skill in the art, and them aligned to known, conserved SRPs to identify suitable probe sequences.

The ability of a particular nucleic acid to hybridize under *given conditions* to a reference nucleic acid is a physical/structural property of the nucleic acid, because it relies upon the nucleotide sequence of the molecule (*see, e.g.*, Sambrook, *Molecular Cloning: A Laboratory Manual*, pp. 9.47-9.51 (2nd ed. 1989); *see also* Stryer, *Biochemistry*, pp. 573 (2nd ed. 1975)). As described in Stryer, the transition between hybridization and melting of complementary nucleic acid strands is abrupt and largely sequence dependent. When the temperature of hybridization is provided, one of skill in the art would be able to predict whether or not a given sequence would hybridize to a reference sequence (*see, e.g.*, equations provided in Sambrook, *supra*).

In the present application, Applicants have provided reference SRP nucleotide sequences, which are highly conserved. Applicants have also defined the claimed oligonucleotide probes through their ability to hybridize under stringent conditions to SRP RNA sequences. As required by the standard set forth in *University of California v. Eli Lilly*, these structural features are common to all of the members of the SRP nucleic acid genus. The SRP conserved sequences, representing the structural features of the genus, and the stringent conditions under which the claimed genus hybridize to such sequences "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (*Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 111, 1116 (Fed. Cir. 1991)). The specification thus appropriately describes the claimed SRP oligonucleotide probe genus using structural/physical features, as required by the court in *University of California v. Eli Lilly*. As such, Applicants respectfully request that the Examiner withdraw the rejection.

Rejection under 35 U.S.C. § 103

Claims 1-2, 4-8, 10-13, 15-16, and 17-19 were rejected as allegedly obvious over Hogan in view of Nakamura, Griffin, Larsen, or Michaeli. Claims 3 and 9 are rejected over the above references, further in view of Rudert. Claims 20-22, 24-25, 28-30, 32, 34, and 39-41 were rejected as allegedly obvious over Hogan in view of Nakamura, Larsen, Griffin, or Michaeli further in view of Jiro. Claims 23 and 26 were rejected over the above-references, further in view of Rudert, Urdea, or Buchardt.

As explained below, the rejection has failed to establish a prima facie case of obviousness for the present application. In order to establish a prima facie case of obviousness, the rejection must demonstrate that (1) the cited references teach all the claimed elements; (2) there is a suggestion or motivation in the prior art to modify or combine the reference teachings; and (3) there is a reasonable expectation of success. MPEP § 2143; *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991). The rejection has failed to indicate that one of skill in the art would have reasonable expectation of success using SRP RNA as a target for detecting selected non-viral organisms. Furthermore, the rejection has failed specifically to identify the principles, known to one of ordinary skill in the art, that suggest the claimed invention (*In re Rouffet*, 47 USPQ2d 1453 (Fed. Cir. 1998)). Therefore, one of skill in the art would not have been motivated to combine the cited references and make the claimed invention.

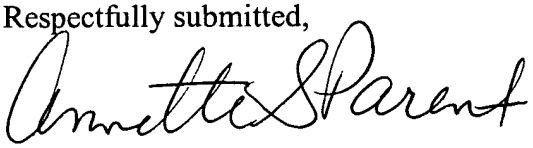
According to the Office Action, Hogan teaches methods for identification of non-viral organisms in samples using hybridization probes to "RNA." However, Applicants would like to note that Hogan actually teaches identification of non-viral organisms in samples using hybridization probes to "ribosomal RNA." In contrast, the present invention is directed to the identification of non-viral organisms in samples using hybridization probes to "signal recognition particle (SRP) RNA." SRP RNA is a unique structural RNA with a distinct cellular function, as compared to rRNA. While rRNA is component of a ribosome, SRP RNA is a component of the signal recognition particle, which recognizes nascent secreted proteins and guides them to the lumen of the endoplasmic reticulum, or in the case of prokaryotes guides proteins to the periplasm.

One of skill in the art would not have a reasonable expectation of success substituting the SRP RNAs of Nakamura, Griffin, Larsen, or Michaeli for the rRNA in the methods of Hogan. Hogan objectively provides no evidence or indication that one of skill in the art would be successful using SRP RNA probes to detect non-viral organisms, nor any evidence nor indication that a correlation can be made between rRNA and SRP RNA, as rRNA and SRP RNA differ in number of significant variables. For example, SRP RNA has a copy number that is substantially lower than the copy number for rRNA. Furthermore, SRP RNA has a conserved secondary structure. Any one such variable has the ability to significantly affect the use of probes to SRP RNA for methods of organism identification. Therefore, one of skill in the art would not have a reasonable expectation of success using SRP RNA in the methods of Hogan. Nor would one of skill in the art be motivated combine the secondary references of the rejection to teach the methods of the present invention. Applicants thus respectfully request that the rejection be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe that all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If the Examiner believes a telephone conference would aid in the prosecution of this case in any way, please call the undersigned at 415-576-0200.

Respectfully submitted,



Annette S. Parent
Reg. No. 42,058

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, 8th Floor
San Francisco, California 94111-3834
(415) 576-0200 / Fax (415) 576-0300